PTO/SB/33 (07-05)
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
078728-0104

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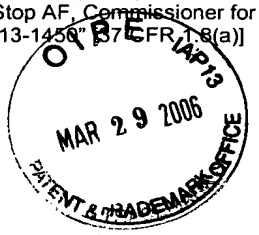

Application Number	Filed
09/972,245	10/09/2001
First Named Inventor: Joseph ROBERTS	
Art Unit: 1635	Examiner: Richard A. Schnizer

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 29,768

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

S. A. Bent
Signature

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March 29, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Joseph ROBERTS, *et al.*

Title: PROTECTING THERAPEUTIC COMPOSITIONS FROM HOST-MEDIATED INACTIVATION

Appl. No.: 09/972,245

Filing Date: 10/09/2001

Examiner: Richard A. Schnizer

Art Unit: 1635

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In accordance with the New **Pre-Appeal Brief Conference Pilot Program**, announced July 11, 2005, this Pre-Appeal Brief Request is being filed together with a Notice of Appeal.

REMARKS

Rejections Under 35 U.S.C. §102

Claims 1-3, 7, 9, 10, 17, 18, 41, 42 and 44 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chinol *et al.* (hereafter "Chinol") (British Journal of Cancer 78(2): 189-197, 1998). In addition, claims 1-3, 7, 9, 10, 17, 18, 41, 42 and 44 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Deckert *et al.* (hereafter "Deckert") (International Journal of Cancer 87:382-390, 2000). Applicants respectfully traverse these rejections.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See generally MPEP §2131.

Applicants submit that none of the cited references discloses "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1. In their last response, Applicants amended step (a) to recite "a biological activity." The subsequent references to "the biological activity" refer to the *same* biological activity referenced in step (a).

With particular regard to Chinol, Applicants note that, in contrast to the presently claimed invention, the authors of the Chinol reference used ELISA to determine the titer of antibodies produced against avidin or mPEG modified avidin and used that to determine that modification of avidin with an average of 7 mPEG reduced the immunogenicity of the protein. Despite the availability of a biological assay namely binding to biotin, they chose to use the ELISA to determine titer of antibody produced as a response to repeated injection to determine the extent of desired modification. Thus, in contrast to Chinol's use of ELISA, according to the presently claimed invention, the biological activity in circulation (as measured by binding to biotin) could be measured as a guide to determine the extent of modification desired to protect avidin from host mediated inactivation instead of using the titer of antibodies produced in animals as a response to variously modified avidin as a guide to determining the desired extent of modification.

Applicants also note that Deckert fails to disclose assaying a first or second modified therapeutic agent after the first or second modified therapeutic agent "has been administered to a subject." While, Deckert used a biological activity, in this case, binding affinity of huA33 to A33 antigen on SW1222 to determine the extent of PEGylation or protein modification. Deckert chose the extent of modification that gave less than 50% loss of binding affinity and determined that 30:1 ratio for PEG 5 and 15:1 for PEG 12 and PEG 20 based on acceptable loss of activity and used these ratios for all subsequent experiments. Thus, the extent of PEGylation was determined solely on acceptable loss of biological activity without the use of in vivo studies.

Deckert's work describes a classical immunogenicity study, in which the authors immunized mice four times with unmodified or huA33 modified at a ratio of 30:1 or huA33 modified at a ratio of 15:1 with PEG20. Antibody titer against unmodified and modified huA33 was determined and they found that animals treated with modified huA33 produced less anti-huA33 antibodies compared to animals treated with unmodified huA33. Two points need to be stressed here. Using two different PEGs, they went into in vivo animal experiment

not to determine the extent of modification but rather to find whether the modifications reduced immunogenicity.

Still further, Applicants note that Deckert measured immunogenicity by determining the titer of anti-huA33 antibodies in treated animals. Interestingly, even though the authors had a biological activity that could have been used to determine the serum concentration of huA33, they did not use that method to determine the titer of huA33 in the serum of treated animal after first and subsequent experiments.

With particular regard to claim 42, Applicants note that neither Chinol nor Deckert discloses "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

With particular regard to claim 44, Applicants note that neither Chinol nor Deckert discloses "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

For the foregoing reasons, Applicants respectfully request review, reconsideration and withdrawal of the outstanding rejections under §102.

Rejections Under 35 U.S.C. §103

Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez *et al.* (hereafter "Alvarez") (Med. Pediatr. Oncol. 34(3):200-205, 2000) in view of Graham *et al.* (hereafter "Graham") (Bone Marrow Transplant (21(9):879-885, 1998), and Francis *et al.* (hereafter "Francis") (Int. J. Hematol. 68(1):1-18, 1998).

Claim 4 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46, and further in view of U.S. Patent 6,531,122 to Petersen *et al.* (hereafter "Petersen").

Claims 8, 11, and 20-22 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13,17, and 41-46, and further in view of Roberts *et al.* (hereafter "Roberts") (J. Gen. Virol. 72:299-305,1991).

Finally, claims 18 and 19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46, and further in view of U.S. Patent 4,678,812 to Bollin et al. (hereinafter "Bollin").

Applicants respectfully traverse each of the foregoing rejections.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.03. Here, no permutation of teachings from the cited publications could have suggested "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent," as recited in claim 1. As discussed above, the references to biological activity in this step relate to the same biological activity.

Further, and with particular regard to Alvarez, Applicants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve the Alvarez's deficiencies. Alvarez used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studies the toxicity of the a particular treatment mode. Alvarez does not report comparison of biological activity of the agent after first and subsequent treatments nor is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis, Petersen, Roberts and Bollin add nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). *See* MPEP 2143.03. Thus, Applicants submit that claims 2-13, 17-22, 41 and 46, which ultimately depend from claim 1, are also non-obvious.

With particular regard to claims 42 and 43, Applicants note that none of the cited references, taken either individually or in combination, teaches or suggests "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

With particular regard to claim 44-45, Applicants note that the cited references, individually or together, do not suggest "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

In view of the foregoing, Applicants respectfully request review, reconsideration and withdrawal of the outstanding rejections under §103.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance.

Respectfully submitted,

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